BMJ Open

Impact of general anaesthesia in overall and disease-free survival compared to other types of anaesthesia in patients undergoing surgery for cutaneous melanoma: A systematic review and meta-analysis protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-027993
Article Type:	Protocol
Date Submitted by the Author:	17-Nov-2018
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Keywords:	Melanoma, Analgesia, Anaesthesia, Cancer, Survival, Recurrence

Title page

Full title: Impact of general anaesthesia in overall and disease-free survival compared to other types of anaesthesia in patients undergoing surgery for cutaneous melanoma: A systematic review and meta-analysis protocol.

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Number of words with references and table: 3513

Number of words without references and table: 2588

Figures: none

References:25

Tables: One

ABSTRACT

Introduction: Cutaneous melanoma is an aggressive type of skin cancer. Anaesthetic agents may have an impact on the immune response, postoperative neurohumoral response, and tumour progression. Experimental data suggest that anaesthetics may influence the postoperative progression of melanoma. This systematic review aims to evaluate the impact of general anaesthesia on overall and disease-free survival compared to other types anaesthesia in patients undergoing surgery for cutaneous melanoma.

Methods and Analysis: The review will analyse data from controlled and observational studies of patients undergoing surgery for melanoma under general anaesthesia compared to other types of anaesthesia. The primary outcomes are 5-year overall survival and 2-year disease-free survival. The secondary outcomes include cost analysis and adverse events. A comprehensive literature search will be performed using the MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science, LILACS, and IBECS databases. Grey literature will also be searched. Risk of methodological bias will be assessed using The Cochrane Collaboration's revised tool for assessing risk of bias in randomised trials (RoB 2.0) and the Newcastle–Ottawa scale for observational studies. Two reviewers will independently assess the eligibility of studies and risk of bias; a third author will solve discrepancies. One author will perform data extraction and the other will check the process and data. Qualitative analysis will be executed using all the included studies. A meta-analysis using a random-effects model for pooled risk estimates will be carried out for the two main outcomes if they conform to previously stated criteria. The GRADE approach will be used to summarise the quality of evidence. EndNote, Rayyan QCRI Cochrane Collaboration's Review Manager (RevMan) software and R software will be used for data management and statistical analysis.

Ethics and Dissemination: Ethics approval is not required as we analyse data from previously reported studies.

PROSPERO registration number: CRD42018114918.

Keywords: Melanoma, Anaesthesia, Analgesia, Cancer, Survival, Recurrence.

ARTICLE SUMMARY

Strengths and limitations of this study

- This review will be the first comprehensive systematic review designed specifically to assess the impact of the anaesthetic technique on overall and disease-free survival in melanoma.
- The results of the systematic review will guide anaesthetists, surgeons, dermatologists, medical oncologists, and patients in clinical decision making.
- The gaps of knowledge in this research field will be addressed, ensuring better research and resource allocation.
- Conclusions and grading of recommendations may be limited by the number and design of included studies.

INTRODUCTION

Cutaneous melanoma is the most lethal form of skin cancer.[1] It is the twenty-first most frequent cancer worldwide with a rising incidence, probably due to the increase in life expectancy.[2] Early stages of melanoma may be cured by excision of primary lesion, but advanced disease is still a challenge despite the recent advances in treatment. There are many factors that lead to a recurrence of cutaneous melanoma after primary surgery. The main prognostic factors are the histologic type, Breslow depth, cutaneous layer invasion (Clark level), regression, mitosis, ulceration on primary lesion, satellite and 'in transit' lesions, lymphatic involvement, and metastatic spread.[3]

Recently, the impact of the anaesthetic technique on recurrence rates of many types of tumours has been a point of intense debate. Retrospective clinical evidence has found a protective effect of some anaesthetics over others in many tumour types, including, but not limited to colon,[4] breast,[5] laryngeal,[6] ovarian,[7] prostate,[8] bladder,[9] and cutaneous melanoma.[10]

Surgery can activate the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis.[11] This leads to an increase in the sympathetic tone, release of adrenocorticotropic hormone (ACTH), and synthesis of corticosteroids and catecholamines by the adrenal gland.[11] Thus, surgery is considered to be an important contributory factor for the clinical evolution of cancer. Inhalational anaesthetics are being investigated as an important facilitator for perioperative tumour dissemination.[12] They may cause inhibition of cellular immunity and promote angiogenesis and cellular proliferation.[13] Basic research in anaesthetic-induced organ protection provides important information regarding cellular signalling, especially, hypoxia-inducible factors (HIFs).[14] Halogenated inhalational anaesthetics can induce HIFs, possibly resulting in a cardiac, cerebral, hepatic, and renal cytoprotection described as 'anaesthetic preconditioning'.[14] The HIF system is essential for adaptation to the reduced supply of oxygen to healthy cells; however, it also helps the continued survival of tumour cells.[14] There is a large body of evidence regarding the relationship of HIFs with cancer.[15]

Experimental data support the hypothesis of anaesthetics influencing melanoma cells. Exposure to halothane and isoflurane, when compared to oxygen, was correlated to an increased number of lung metastasis in C57BL mice model injected with B16 melanoma cells.[16] In contrast, propofol induced

apoptosis of B16F10 melanoma cells 'in vitro'.[17] Lidocaine and ropivacaine reduced the viability of melanoma cells and increased apoptosis in a concentration-dependent manner 'in vitro'.[18]

Changes in institutional anaesthesia protocols to avoid general anaesthesia can impact the cost and the overall safety of surgical procedure. Therefore, a systematic review and analysis of overall and disease-free survival may modify clinical practice. This systematic review may influence the choice of anaesthetic technique among anaesthetists, dermatologists, surgical oncologists, and patients.

The main objective of the proposed study is to evaluate the relationship between the anaesthetic technique and the overall and disease-free survival of malignant melanoma patients undergoing surgical resection. The question formulated to fulfil the study objective is: Does general anaesthesia imply worse overall or disease-free survival rate compared to other types of anaesthesia in patients undergoing surgery for cutaneous melanoma? The secondary objectives are cost assessment and adverse events.

The systematic review protocol was designed according to the PRISMA-P statement.[19] The MOOSE proposal for reporting observational studies was also used as a reference for protocol development.[20] This systematic review has no specific funding. The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 16 November 2018 and was not updated (registration number CRD42018114918). In case of a protocol amendment, it will be described in detail, including the date and the rationale, and reported in the PROSPERO database.

METHODS AND ANALYSIS

Eligibility criteria

Participants

The systematic review will include human studies evaluating patients undergoing surgery for cutaneous melanoma. Non-cutaneous melanomas will not be included in the review. If the term 'melanoma' is included in the text of the manuscript, it will be assumed to imply cutaneous melanoma, since it is the most frequent subtype of the disease. Studies with less than 10 participants on each arm will be excluded. No age, sex, or race restrictions will be applied. In case of studies that involve the overlap of patients, only the most recent article will be chosen for inclusion.

Study design

Randomised controlled trials (RCT) and observational studies (case control or cohort studies) will be included in the final analysis.

Interventions

To be included in the review, the study must report a comparison of patients who undergo general anaesthesia with other types of anaesthesia. Techniques other than general anaesthesia will be aggregated as a single group in each study.

Outcomes

The aim is to assess if the use of general anaesthesia results in a higher risk of death or recurrence in melanoma patients. The main outcomes are 5-year overall survival and 2-year disease-free survival. Cost analysis and adverse events will be the secondary outcomes. Outcomes are not part of the eligibility criteria to be included in the review. Results of individual studies not including predefined outcomes will be reported in the body of the article or in an appendix according to the authors conclusions regarding the relevance of individual studies.

Timing

No timing restriction will be applied. All potentially relevant articles available in the selected databases will be included in the review.

Setting and language

The initial triage of articles will require a title in English. No other language restrictions will be applied and articles in other languages will be translated when necessary for analysing eligibility criteria, evaluating risk of bias, and data extraction. The authors of the original articles will be contacted when deemed necessary, first by email, and then through other digital platforms (e.g. LinkedIn, ORCID and ResearchGate) and correspondence.

Information sources

The main electronic databases accessed will be MEDLINE (PubMed interface), Excerpta Medica database (EMBASE), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (online search engine, using all available databases), Latin American and Caribbean Health Sciences Literature (in Portuguese: *Literatura Latino-Americana e do Caribe em Ciências da Saúde* – LILACS), and The Spanish Bibliographic Index of the Health Sciences (in Spanish: *Índice Bibliográfico Español en Ciencias de la Salud* - IBECS). We will include studies published from the start of indexing until 30 October 2018.

Other sources

Hand searches of the first 200 citations on Google Scholar will be performed. Reference lists of the included articles, reviews, and citing articles searched using the Web of Science database will be checked. Grey literature will be searched using the Open Grey (http://www.opengrey.eu) and the Open Access Theses and Dissertations (https://oatd.org) registries. The International Clinical Trials Registry Platform search portal (http://apps.who.int/trialsearch) will also be accessed.

Search strategy

Search terms are designed to address the Patient, Intervention, Comparison, Outcome (PICO) standards. Patients will be searched using melanoma-related terms. For interventions and comparisons, anaesthesia related terms will be used. The authors of the systematic review decided to exclude the outcomes and any specific term related to the study design to increase the sensitivity of the search strategy. The specific search strategies were developed by one author (BLCA) and reviewed by a Health Science Librarian with expertise in systematic review searches. MEDLINE, EMBASE, and LILACS searches were chosen according to specific Medical Subject Headings (MeSH), Embase subject headings (Emtree) and Health Sciences Descriptors (in Portuguese: *Descritores em Ciências da Saúde* – DeCS) terms respectively. The search strategy for PubMed is described in Table 1 and the complete search strategies are reported in Appendix 1.

Table 1 PubMed search strategy

Database	Search

PubMed	1 Anesthesia[MeSH Terms] 2 Anesthetics[MeSH Terms] 3 Anesthesiology[MeSH Terms] 4 Anest*[Title/Abstract] 5 Anaest*[Title/Abstract] 6 Analg*[Title/Abstract] 7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 8 Melanoma[MeSH Terms] 9 Melanoma*[Title/Abstract] 10 #8 OR #9 11 #7 AND #10

Data Management

EndNote web will be used for reference management; Rayyan (Qatar Computing Research Institute - QCRI) web application will be used for the process of selection of studies. Cochrane Collaboration's Review Manager (RevMan) software and R software will be used for systematic review data management and statistical analysis.

Selection of Studies

Two authors (BLCA and JOL) will check all the references in the databases. Independent evaluation will be carried out using a stepwise approach for screening, eligibility, and inclusion of studies. Concordance will be assessed by the kappa statistic in each step and reported. In the screening phase, articles selected by at least one of the authors will be submitted to full-text evaluation in the eligibility phase if a consensus is not reached between authors. Disagreements will be resolved by consensus or at the

discretion of the senior researcher (LCST). One review author (BLCA) will extract the data to the RevMan software and a second author (JLO) will check the process and the data collected.

Risk of Bias

The Cochrane Collaboration's revised tool for assessing the risk of bias in randomised trials (RoB 2.0) will be used to evaluate RCT; the Newcastle-Ottawa scale will be used to assess methodological bias in observational studies. The risk of bias assessment will be conducted by two authors (BLCA and JLO); in case of disagreement, a third author (LCST) will arbitrate. The summary of the assessment of the risk of bias in each category will be reported.

Publication Bias

If ten or more studies are included in the systematic review, a funnel plot visual analysis will be performed for publication bias assessment.

Heterogeneity

Statistical heterogeneity will be assessed using Chi-squared (χ^2) and inconsistency (I^2) tests. Heterogeneity will be quantified by the I^2 test described in the Cochrane Handbook for Systematic Reviews of Interventions and will be reported as low (I^2=0-25%), moderate (I^2 =26-50%), or high (I2>50%).[21] If, according to the judgement of the reviewers, clinical, methodological, and statistical heterogeneities make pooling of data inappropriate for a specific outcome, the meta-analysis will be omitted for this outcome. However, data of individual studies will be displayed as a forest plot for a better appraisal of the results.

Qualitative analysis

Studies included in the review evaluating overall survival, disease-free survival, costs, and adverse events as endpoints will be summarised in tables including authorship, year of publication, study sample, design, interventions or arms, comparisons, reported outcomes, and results. Other details regarding study design and quality of reports will also be described, addressing the strengths and weaknesses of the body of evidence and how they impact the interpretation of the results of the meta-analysis.

Quantitative analysis

Overall and disease-free survival analysis will be quantitatively evaluated if more than one study is included for a specific endpoint. For RCT and cohort studies data will be pooled based on relative risk estimation; adjusted data will be used to reduce confounding risk in observational studies if possible. Effect size will be measured with 95% confidence intervals (CI), and significance will be set at $P < 0.05$, with the study as the unit of analysis. Case-control studies will be reported using odds ratio as the summary measure, and the data from this type of studies will be reported separately. If it is not possible to extract relative risk data from other sources, Kaplan-Meyer curves will be the source of the data, using a pixel-coordinate method of mapping the axes of interest and calculation of percentages. A broad definition regarding patient selection in studies will be used, permitting the inclusion of different stages, surgical procedures, and control groups between studies. A random effects model will be chosen to perform the meta-analysis considering anticipated clinical and methodological heterogeneity. If 5-year overall survival is reported, it will be the preferred follow-up period for relative risk analysis. If 5-year survival is not reported, we will attempt to contact the authors for this information; if no contact is possible, the longest reported follow-up period will be chosen. Two-year disease-free survival will be chosen as the other study outcome. These preferred periods of follow-up were chosen according to recent recommendations regarding postoperative cancer outcomes.[22] Results will be aggregated independent to the duration of follow-up. The inclusion of trials outside the target follow-up period will increase the power of the review without impacting the goals of the review. A sensitivity analysis will be performed excluding studies with follow-up periods other than 5-year overall and 2-year disease-free survival. Sensitivity analysis will also be carried out after excluding studies that are observational in design and assessed to have a high risk of bias to evaluate the impact of clinical and methodological heterogeneity on outcomes. The year of publication (to assess changes in therapy over time) and the anaesthetic technique used in the control group (local, regional, and both) will be used as parameters to perform a meta-regression and subgroup analysis.

Quality of the Body of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarise the quality of evidence for each outcome will be applied.[23] The GRADE rating scale assigns high, moderate, low, or very low reliability categories to a body of evidence as detailed elsewhere. [23]

Discussion

Some of the previous systematic reviews investigating the relationship between exposure to anaesthetic agents on survival and oncologic outcomes included different cancer types and anaesthetic agents in the same evaluation.[24, 25] Cancer cannot be treated as a single disease or a group of diseases with a similar response to various treatment modalities. Therefore, systematic reviews on this topic should consider relevance to specific types of cancer regarding tumour biology and specific surgical techniques employed, despite the lack of prospective studies in this field.

The inclusion of cohort and case-control studies in the systematic review may be an expected source of bias. The association between anaesthetic technique and oncologic outcomes is not an anticipated endpoint of therapy; we aim to assess the possibility of unexpected harm in this systematic review. Unequivocal evidence of association of the anaesthetic technique with survival outcomes through randomised controlled trials may take several decades to establish. Such studies are expensive, take a long period of time, and require extensive follow-up. Hence, they are usually outside the scope of regular anaesthesia research. Decision-making is complex in the absence of such high-quality evidence, because evidence of harm is difficult to establish, though harm may occur in some instances. Therefore, observational data must be carefully assessed, especially when prospective data is inadequate. Adjusted data from observational studies by pooled-analysis will be used to overcome confounding factors. Subgroup analyses will address the influence of different study designs on the effect measure of this meta-analysis.

A recent consensus of experts in the field of anaesthesiology defined the main outcomes to be chosen when evaluating the impact of anaesthesia techniques on cancer outcomes.[22] The endpoints chosen for this systematic review are based on this report. A uniform definition of outcomes of interest is essential to carry out future observational studies and clinical trial protocols.

ETHICS AND DISSEMINATION

This study is a systematic review with meta-analysis that evaluates data from previously reported studies; hence ethical approval is not required. We plan to publish this study in a peer-reviewed journal.

Author Contributions: BLCA is the guarantor of the review and drafted the manuscript. All authors contributed to the inclusion criteria, the risk of bias assessment, and data extraction strategies. FMC and LESF contributed with their knowledge on systematic reviews. LCST and FMC will contribute with

epidemiological and statistical analysis. ACM contributed through expertise in medical, and JLO, through expertise in surgical oncology. BLCA contributed with anaesthetic knowledge. BLCA and JLO will screen potential studies, perform duplicate independent data extraction, risk of bias assessment, GRADE assessment. LCST will act as a third reviewer and arbitrator if necessary. All authors read, provided comments, and approved the final version of the protocol.

Acknowledgements: We are grateful to acknowledge to Raphael Chanca, the Health Science Librarian who reviewed the systematic review search strategy.

Funding: The authors have not received a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: None declared.

Patient consent: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data from this study are available.

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Appendix 1

Complete search Strategy

Database	Search
Pubmed	1 Anesthesia[MeSH Terms] 2 Anesthetics[MeSH Terms] 3 Anesthesiology[MeSH Terms] 4 Anest*[Title/Abstract] 5 Anaest*[Title/Abstract] 6 Analg*[Title/Abstract] 7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 8 Melanoma[MeSH Terms] 9 Melanoma*[Title/Abstract] 10 #8 OR #9 11 #7 AND #10
Embase	1 'melanoma'/exp 2 'fortner melanoma':ti,ab 3 'malignant melanoma':ti,ab 4 'malignant melanomatosis':ti,ab 5 'melanocarcinoma':ti,ab 6 'melanoma':ti,ab 7 'melanoma (e)':ti,ab 8 'melanomalignoma':ti,ab 9 'naevi and melanomas':ti,ab 10 'naevocarcinoma':ti,ab 11 'nevi and melanomas':ti,ab 12 'nevocarcinoma':ti,ab 13 'nodular melanoma':ti,ab 14 'pigmentary cancer':ti,ab 15 #1 OR# 2 OR #3 OR #4# OR # 5# OR #6# OR# 7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

	16	'anesthesiological procedure'/exp
	17	'anaesthesia and analgesia':ti,ab
	18	'anesthesia and analgesia':ti,ab
	19	'anesthesiological procedure':ti,ab
	20	'anesthesiological techniques':ti,ab
	21	'anesthetic agent'/exp
	22	'anaesthetic':ti,ab
	23	'anaesthetic agent':ti,ab
	24	'anaesthetic drug':ti,ab
	25	'anaesthetics':ti,ab
	26	'anaesthetics, combined':ti,ab
	27	'anaesthetics, dissociative':ti,ab
	28	'anaesthetics, general':ti,ab
	29	'anesthetic':ti,ab
	30	'anesthetic agent':ti,ab
	31	'anesthetic drug':ti,ab
	32	'anesthetics':ti,ab
	33	'anesthetics, combined':ti,ab
	34	'anesthetics, dissociative':ti,ab
	35	'anesthetics, general':ti,ab
	36	'general anaesthetic':ti,ab
	37	'general anaesthetic agent':ti,ab
	38	'general anesthetic':ti,ab
	39	'general anesthetic agent':ti,ab
	40	(#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39)
	41	#15 AND #40
CENTRAL	1	MeSH descriptor: [Anesthesia] explode all trees
	2	MeSH descriptor: [Anesthetics] explode all trees
	3	MeSH descriptor: [Anesthesiology] explode all trees

	4 Anest*:ab,ti,kw
	5 Anaest*:ab,ti,kw
	6 #1 OR #2 OR #3 OR #4 OR #5
	7 MeSH descriptor: [Melanoma] explode all trees
	8 Melanoma*:ab,ti,kw
	9 #7 OR #8
	10 #6 AND #9
Web of science	1 TS=(Anest* OR Anaest*)
	2 TS=(Melanoma*)
	3 #1 AND #2
Virtual Health Library Portal (LILACS and IBECS)	1 mh:("anesthesia")
	2 mh:("anesthesia and analgesia")
	3 mh:("analgesia and anesthesia")
	4 mh:("analgesia")
	5 tw:(anest*)
	6 tw:(analg*)
	7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
	8 mh:(Melanoma)
	9 tw:(Melanoma*)
	10 #8 OR #9
	11 #7 AND #10
International Clinical Trials Registry Platform Portal	In the Advanced Search Title: Anest* OR Anaest* OR Analg* Condition: Melanoma Recruitment status: All
OpenGrey	1 Anest*
	2 Anaest*
	3 Analg*
	4 #1 OR #2 OR #3
	5 Melanoma*
	6 #4 AND #5

Open Access Theses and Dissertations	1 Anest* 2 Anaest* 3 Analg* 4 #1 OR #2 OR #3 5 Melanoma* 6 #4 AND #5
Google Scholar	anesthesia AND melanoma

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	3-5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☒	☐	115,116
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	61
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	7-32
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	267-274
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	116-117
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	114
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	114
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	114
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	74-102
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	107-111
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	119-149
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	150-163
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	164-175
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	176-180
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	181-188
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	181-188
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	206-230
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	134-140
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	189-194
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	206-211
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	198-202; 212-230
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	230-236
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	202-205
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	195-197
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	223-240

BMJ Open

Impact of general anaesthesia in overall and disease-free survival compared to other types of anaesthesia in patients undergoing surgery for cutaneous melanoma: A systematic review and meta-analysis protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-027993.R1
Article Type:	Protocol
Date Submitted by the Author:	22-May-2019
Complete List of Authors:	Araujo, Bruno; National Cancer Institute of Brazil , Anaesthesiology - Hospital do Câncer II de Oliveira, Jadivan; National Cancer Institute of Brazil , Conective and Bone Tissue Section, Hospital do Câncer II Corrêa, Flavia; National Cancer Institute of Brazil , Health Technology Assessment Unit, Population Research Division Fontes, Luis; Petrópolis Medical School, Department of Evidence-Based Medicine, Intensive Care, Gastroenterology de Melo, Andreia; National Cancer Institute of Brazil , Clinical Research Division, National Cancer Institute of Brazil (INCA) Thuler, Luiz; Brazilian National Cancer Institute , Clinical Research Division; Federal University of Rio de Janeiro State, Postgraduate Program in Neurosciences
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Surgery, Dermatology, Oncology
Keywords:	Melanoma, Analgesia, Anaesthesia, Cancer, Survival, Recurrence

Title page

Full title: Impact of general anaesthesia in overall and disease-free survival compared to other types of anaesthesia in patients undergoing surgery for cutaneous melanoma: A systematic review and meta-analysis protocol.

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Number of words with references and table: 4004

Number of words without references and table: 2993

Figures: none

References: 28

Tables: One

ABSTRACT

Introduction: Cutaneous melanoma is an aggressive type of skin cancer. Anaesthetic agents may have an impact on the immune response, postoperative neurohumoral response, and tumour progression. This systematic review aims to evaluate the impact of general anaesthesia on overall and disease-free survival compared to other types anaesthesia in patients undergoing surgery for cutaneous melanoma.

Methods and analysis: The review will analyse data from controlled and observational studies of patients undergoing surgery for melanoma under general anaesthesia compared to other types of anaesthesia. The primary outcomes are overall survival and disease-free survival. The secondary outcomes are health-related quality of life, time to tumour progression, distant disease-free survival, time to treatment failure, cancer-specific survival, biochemical recurrence, return of intended oncologic therapy, days alive and out of the hospital at 90 days, cost analysis, and adverse events. A comprehensive literature search will be performed using the MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science, LILACS, and IBECS databases. Grey literature will also be searched. Risk of methodological bias will be assessed using The Cochrane Collaboration's revised tool for assessing risk of bias in randomised trials (RoB 2.0) and the Newcastle–Ottawa scale. Two reviewers will independently assess the eligibility of studies and risk of bias; a third author will solve discrepancies. One author will perform data extraction and the other will check the process and data. Qualitative analysis will be carried out using all included studies. A meta-analysis using a random-effects model for pooled risk estimates will be carried out for the two main outcomes and for selected secondary outcomes if they conform to previously stated criteria. The GRADE approach will be used to summarise the quality of evidence.

Ethics and dissemination: Ethics approval is not required as we analyse data from previously reported studies.

PROSPERO registration number: CRD42018114918.

Keywords: Melanoma, Anaesthesia, Analgesia, Cancer, Survival, Recurrence.

ARTICLE SUMMARY

Strengths and limitations of this study

- This will be the first comprehensive systematic review designed specifically to assess the impact of anaesthetic technique on overall and disease-free survival in melanoma.
- The inclusion of non-randomised studies is both a strength and a limitation of the protocol.
- Observational studies will not be combined with randomised controlled trials and quasi-randomised trials, limiting the influence of study design on the effects measured in this meta-analysis.
- A rigorous and sensitive search will be performed to maximise comprehensiveness and minimise bias.
- The Grading of Recommendations, Assessment, Development and Evaluation approach will be used to inform conclusions in an appropriate manner.

INTRODUCTION

Cutaneous melanoma is the most lethal form of skin cancer.[1] It is the twenty-first most frequent cancer worldwide with a rising incidence, probably due to the increase in life expectancy.[2] Early stages of melanoma may be cured by excision of primary lesion, but advanced disease is still a challenge despite the recent advances in treatment. There are many factors that lead to a recurrence of cutaneous melanoma after primary surgery. The main prognostic factors are the histologic type, Breslow depth, cutaneous layer invasion (Clark level), regression, mitosis, ulceration on primary lesion, satellite and 'in transit' lesions, lymphatic involvement, and metastatic spread.[3]

Recently, the impact of the anaesthetic technique on recurrence rates of many types of tumours has been a point of intense debate. Retrospective clinical evidence has found a protective effect of some anaesthetics over others in many tumour types, including, but not limited to colon,[4] breast,[5] laryngeal,[6] ovarian,[7] prostate,[8] bladder,[9] and cutaneous melanoma.[10]

Surgery can activate the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis.[11] This leads to an increase in the sympathetic tone, release of adrenocorticotropic hormone, and synthesis of corticosteroids and catecholamines by the adrenal gland.[11] Thus, surgery is considered to be an important contributory factor for the clinical evolution of cancer. Inhalational anaesthetics are being investigated as an important facilitator for perioperative tumour dissemination.[12] They may cause inhibition of cellular immunity and promote angiogenesis and cellular proliferation.[13] Basic research in anaesthetic-induced organ protection provides important information regarding cellular signalling, especially, hypoxia-inducible factors (HIFs).[14] Halogenated inhalational anaesthetics can induce HIFs, possibly resulting in a cardiac, cerebral, hepatic, and renal cytoprotection described as 'anaesthetic preconditioning'.[14] The HIF system is essential for adaptation to the reduced supply of oxygen to healthy cells; however, it also helps the continued survival of tumour cells.[14] There is a large body of evidence regarding the relationship of HIFs with cancer.[15]

Experimental data support the hypothesis of anaesthetics influencing melanoma cells. Exposure to halothane and isoflurane, when compared to oxygen, was correlated to an increased number of lung metastasis in C57BL mice model injected with B16 melanoma cells.[16] In contrast, propofol induced apoptosis of B16F10 melanoma cells 'in vitro'.[17] Lidocaine and ropivacaine reduced the viability of

melanoma cells and increased apoptosis in a concentration-dependent manner 'in vitro'.[18] The first report of impaired survival associated with the use of general anaesthesia for melanoma surgery was published by Seebacher *et al*; subsequent investigators achieved conflicting results.[10,19-21]

Changes in institutional anaesthesia protocols to avoid general anaesthesia can impact the cost and the overall safety of surgical procedure. Therefore, a systematic review and analysis of overall and disease-free survival may modify clinical practice. This systematic review may influence the choice of anaesthetic technique among anaesthetists, dermatologists, surgical oncologists, and patients.

The main objective of the proposed study is to evaluate the relationship between the anaesthetic technique and the overall and disease-free survival of malignant melanoma patients undergoing surgical resection. The question formulated to fulfil the study objective is: Does general anaesthesia imply worse overall or disease-free survival rate compared to other types of anaesthesia in patients undergoing surgery for cutaneous melanoma? The secondary objectives are assessment of health-related quality of life, time to tumour progression, distant disease-free survival, time to treatment failure, cancer-specific survival, biochemical recurrence, return of intended oncologic therapy, days alive and out of the hospital at 90 days, costs, and adverse events.

This systematic review protocol was designed in accordance with the PRISMA-P statement.[22] The MOOSE proposal for reporting observational studies was also used as a reference for protocol development.[23] This systematic review has no specific funding. The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 16 November 2018 and has not been updated (registration number CRD42018114918). A protocol amendment with the modifications of the systematic review protocol following the peer reviewduring the *BMJ Open* editorial process will be described in detail, including the date and the rationale; this will be reported in the PROSPERO database.

METHODS AND ANALYSIS

Eligibility criteria

Participants

The systematic review will include human studies evaluating patients undergoing surgery for cutaneous melanoma. Non-cutaneous melanomas will not be included in the review. If the term 'melanoma' is included in the text of the manuscript, it will be assumed to imply cutaneous melanoma, since it is the most frequent subtype of the disease. Studies with fewer than 10 participants on each arm will be excluded. No age, sex, or race restrictions will be applied. In case of studies that involve the overlap of patients, only the most recent article will be chosen for inclusion.

Study design

Randomised controlled trials (RCTs), quasi-randomised trials, and non-randomised studies (cohort and case–control studies) will be included in the final analysis.

Interventions

To be included in the review, the study must report a comparison of patients who underwent general anaesthesia with other types of anaesthesia. Techniques other than general anaesthesia will be aggregated as a single group in each study.

Outcomes

The aim is to assess if the use of general anaesthesia results in a higher risk of death or recurrence in melanoma patients. The primary outcomes are overall survival and disease-free survival. The secondary ouctomes are health-related quality of life, time to tumour progression, distant disease-free survival, time to treatment failure, cancer-specific survival, biochemical recurrence, return of intended oncologic therapy, days alive and out of the hospital at 90 days, cost analysis, and adverse events. Outcomes are not part of the eligibility criteria to be included in the review. Results of individual studies not including predefined outcomes will be reported in the body of the article or in an appendix according to the authors conclusions regarding the relevance of individual studies.

Timing

No timing restriction will be applied. All potentially relevant articles available in the selected databases will be included in the review.

Setting and language

The initial triage of articles will require a title in English. No other language restrictions will be applied and articles in other languages will be translated when necessary for analysing eligibility criteria, evaluating risk of bias, and data extraction. The authors of the original articles will be contacted when deemed necessary, first by email, and then through other digital platforms (e.g. LinkedIn, ORCID and ResearchGate) and correspondence.

Information sources

The main electronic databases accessed will be MEDLINE (PubMed interface), Excerpta Medica database (EMBASE), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (online search engine, using all available databases), Latin American and Caribbean Health Sciences Literature (in Portuguese: *Literatura Latino-Americana e do Caribe em Ciências da Saúde* – LILACS), and The Spanish Bibliographic Index of the Health Sciences (in Spanish: *Índice Bibliográfico Español en Ciencias de la Salud* - IBECS). We will include studies published from the start of indexing until 30 October 2018.

Other sources

Hand searches of the first 200 citations on Google Scholar will be performed. Reference lists of the included articles, reviews, and citing articles searched using the Web of Science database will be checked. Grey literature will be searched using the Open Grey (http://www.opengrey.eu) and the Open Access Theses and Dissertations (https://oatd.org) registries. The International Clinical Trials Registry Platform search portal (http://apps.who.int/trialsearch) will also be accessed.

Search strategy

Search terms are designed to address the Patient, Intervention, Comparison, Outcome (PICO) standards. Patients will be searched using melanoma-related terms. For interventions and comparisons, anaesthesia related terms will be used. The authors of the systematic review decided to exclude the outcomes and any specific term related to the study design to increase the sensitivity of the search strategy. The specific search strategies were developed by one author (BLCA) and reviewed by a Health Science Librarian with expertise in systematic review searches. MEDLINE, EMBASE, and LILACS searches were chosen according to specific Medical Subject Headings (MeSH), Embase subject headings (Emtree) and Health

Sciences Descriptors (in Portuguese: *Descritores em Ciências da Saúde* – DeCS) terms, respectively. The search strategy for PubMed is described in Table 1 and the complete search strategies are reported in Appendix 1.

Table 1 PubMed search strategy

Database	Search
PubMed	1 Anesthesia[MeSH Terms]
	2 Anesthetics[MeSH Terms]
	3 Anesthesiology[MeSH Terms]
	4 Anest*[Title/Abstract]
	5 Anaest*[Title/Abstract]
	6 Analg*[Title/Abstract]
	7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
	8 Melanoma[MeSH Terms]
	9 Melanoma*[Title/Abstract]
	10 #8 OR #9
	11 #7 AND #10

Data Management

EndNote web will be used for reference management; Rayyan (Qatar Computing Research Institute - QCRI) web application will be used for the process of selection of studies. Cochrane Collaboration's Review Manager (RevMan) software and R software will be used for systematic review data management and statistical analysis.

Selection of Studies

Two authors (BLCA and JOL) will check all the references in the databases. Independent evaluation will be carried out using a stepwise approach for screening, eligibility, and inclusion of studies. Interrater agreement within the screening process will be assessed by using Cohen's kappa statistic in each step and reported.[24] In the screening phase, articles selected by at least one of the authors will be submitted to full-text evaluation in the eligibility phase if a consensus is not reached between authors. Disagreements will be resolved by consensus or at the discretion of the senior researcher (LCST). One review author (BLCA) will extract the data to the RevMan software and a second author (JLO) will check the process and the data collected.

Risk of Bias

The Cochrane Collaboration's revised tool for assessing the risk of bias in randomised trials (RoB 2.0) will be used to evaluate RCTs; the Newcastle-Ottawa scale will be used to assess methodological bias in observational studies. The risk of bias assessment will be conducted by two authors (BLCA and JLO); in case of disagreement, a third author (LCST) will arbitrate. The summary of the assessment of the risk of bias in each category will be reported.

Publication Bias

If ten or more studies are included in the systematic review, a funnel plot visual analysis will be performed for publication bias assessment.

Heterogeneity

Statistical heterogeneity will be assessed using Chi-squared (χ^2) and inconsistency (I^2) tests. Heterogeneity will be quantified by the I^2 test described in the Cochrane Handbook for Systematic Reviews of Interventions and will be reported as low (I^2=0-25%), moderate (I^2 =26-50%), or high (I2>50).[24] If, according to the judgement of the reviewers, clinical, methodological, and statistical heterogeneities make pooling of data inappropriate for a specific outcome, the meta-analysis will be omitted for this outcome. However, data of individual studies will be displayed as a forest plot for a better appraisal of the results.

Qualitative analysis

The studies included in the review evaluating the primary and secondary outcomes will be summarised in tables including authorship, year of publication, study sample, design, interventions or arms, comparisons, reported outcomes, and results. Other details regarding study design and quality of reports will also be described, addressing the strengths and weaknesses of the body of evidence and how they impact the interpretation of the results of the meta-analysis.

Quantitative analysis

RCTs and quasi-randomised trials will be pooled separately from observational studies for meta-analysis to reduce methodological heterogeneity. Overall and disease-free survival analysis will be quantitatively evaluated if more than one study with the same design is included for a specific endpoint. A meta-analysis will also be performed if more than one study reports the secondary outcomes time to tumour progression, distant disease-free survival, time to treatment failure, cancer specific survival, return of intended oncologic therapy, and days alive and out of hospital at 90 days. Hazards ratio (HR) estimation will be used as the summary measure for RCTs, quasi-randomised trials, and cohort studies; however, days alive out and of the hospital at 90 days will be evaluated using odds ratios, independent of study design. Case–control studies will be reported using odds ratios as the summary measure, and the data from this type of study will be reported separately. Effect size will be measured with 95% confidence intervals, and significance will be set at $P<0.05$, with the study as the unit of analysis. Adjusted data will be used if available, to reduce the risk of confounding in observational studies. The use of an adjusted estimate has a higher priority than requiring a similar period of follow-up across studies, because reduction of confounding factors is critical in ensuring the generality of the results. If it is not possible to extract HR data from other sources, Kaplan–Meier curves will be the source of the data, using a pixel-coordinate method of mapping the axes of interest and calculation of percentages. If 5-year overall survival is reported, it will be the preferred follow-up period for HR analysis. When 5-year survival is not reported, we will attempt to contact the authors for this information; if no contact is possible, the longest reported follow-up period will be chosen. Two-year disease-free survival will be used as the other study outcome. These preferred periods of follow-up were chosen in accordance with recent recommendations for analyses of postoperative cancer outcomes.[25] For the secondary outcomes of time-to-event data, the longest reported follow-up period will be used. Minimum follow-up required to be included in the meta-analysis for the time-to event data is estimated at 2 years. Results will be aggregated independent of the

duration of follow-up if longer than 2 years. The inclusion of trials outside the target follow-up period will increase the power of the review without impacting the goals of the review. A broad definition regarding patient selection in studies will be used, permitting the inclusion of different stages, surgical procedures, and control groups between studies. A random effects model will be used to perform the meta-analysis, considering the anticipated clinical and methodological heterogeneity. A sensitivity analysis will be performed excluding studies with follow-up periods other than 5-year overall and 2-year disease-free survival. Sensitivity analysis will also be carried out after excluding studies that are judged to have a risk of bias to evaluate the impact of clinical and methodological heterogeneity on outcomes. The year of publication (to assess changes in therapy over time) and the anaesthetic technique used in the control group (local, regional, and both) will be used as parameters to perform a meta-regression and subgroup analysis.

Quality of the Body of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarise the quality of evidence for each outcome will be applied.[26] The GRADE rating scale assigns high, moderate, low, or very low reliability categories to a body of evidence as detailed elsewhere.[26]

DISCUSSION

Some of the previous systematic reviews investigating the relationship between exposure to anaesthetic agents on survival and oncologic outcomes included different cancer types and anaesthetic agents in the same evaluation.[27, 28] Cancer cannot be treated as a single disease or a group of diseases with a similar response to various treatment modalities. Therefore, systematic reviews on this topic should consider relevance to specific types of cancer regarding tumour biology and specific surgical techniques employed, despite the lack of prospective studies in this field.

The inclusion of cohort and case–control studies in the systematic review may be an expected source of bias. The association between anaesthetic technique and oncologic outcomes is not an anticipated endpoint of therapy; we aim to assess the possibility of unexpected harm in this systematic review. Unequivocal evidence of association of the anaesthetic technique with survival outcomes through randomised controlled trials may take several decades to establish. Such studies are expensive, take a long period of time, and require extensive follow-up. Hence, they are usually outside the scope of regular

anaesthesia research. Decision-making is complex in the absence of such high-quality evidence, because evidence of harm is difficult to establish, though harm may occur in some instances. Therefore, observational data must be carefully assessed, especially when prospective data is inadequate. Adjusted data from observational studies by pooled analysis will be used to overcome confounding factors. Observational studies will not be combined with RCTs or quasi-randomised trials, limiting the influence of study design on the effects measured by this meta-analysis.

A recent consensus of experts in the field of anaesthesiology defined the main outcomes to be chosen when evaluating the impact of anaesthesia techniques on cancer outcomes.[25] The endpoints chosen for this systematic review are based on this report. A uniform definition of outcomes of interest is essential to carry out future observational studies and clinical trial protocols.

ETHICS AND DISSEMINATION

This study is a systematic review with meta-analysis that evaluates data from previously reported studies; hence ethical approval is not required. We plan to publish this study in a peer-reviewed journal.

Author Contributions: BLCA is the guarantor of the review and drafted the manuscript. All authors contributed to the inclusion criteria, the risk of bias assessment, and data extraction strategies. FMC and LESF contributed with their knowledge on systematic reviews. LCST and FMC will contribute with epidemiological and statistical analysis. ACM contributed through expertise in medical, and JLO, through expertise in surgical oncology. BLCA contributed with anaesthetic knowledge. BLCA and JLO will screen potential studies, perform duplicate independent data extraction, risk of bias assessment, GRADE assessment. LCST will act as a third reviewer and arbitrator if necessary. All authors read, provided comments, and approved the final version of the protocol.

Acknowledgements: We are grateful to acknowledge to Raphael Chanca, the Health Science Librarian who reviewed the systematic review search strategy.

Funding: The authors have not received a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: None declared.

Patient consent: Not required.

Patient and public involvement: Patients and public were not involved in the development of this systematic review protocol.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data from this study are available.

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Appendix 1

Complete search Strategy

Database	Search	
Pubmed	1	Anesthesia[MeSH Terms]
	2	Anesthetics[MeSH Terms]
	3	Anesthesiology[MeSH Terms]
	4	Anest*[Title/Abstract]
	5	Anaest*[Title/Abstract]
	6	Analg*[Title/Abstract]
	7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
	8	Melanoma[MeSH Terms]
	9	Melanoma*[Title/Abstract]
	10	#8 OR #9
	11	#7 AND #10
Embase	1	'melanoma'/exp
	2	'fortner melanoma':ti,ab
	3	'malignant melanoma':ti,ab
	4	'malignant melanomatosis':ti,ab
	5	'melanocarcinoma':ti,ab
	6	'melanoma':ti,ab
	7	'melanoma (e)':ti,ab
	8	'melanomalignoma':ti,ab
	9	'naevi and melanomas':ti,ab
	10	'naevocarcinoma':ti,ab
	11	'nevi and melanomas':ti,ab
	12	'nevocarcinoma':ti,ab
	13	'nodular melanoma':ti,ab
	14	'pigmentary cancer':ti,ab
	15	#1 OR# 2 OR #3 OR #4# OR # 5# OR #6# OR# 7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

	16	'anesthesiological procedure'/exp
	17	'anaesthesia and analgesia':ti,ab
	18	'anesthesia and analgesia':ti,ab
	19	'anesthesiological procedure':ti,ab
	20	'anesthesiological techniques':ti,ab
	21	'anesthetic agent'/exp
	22	'anaesthetic':ti,ab
	23	'anaesthetic agent':ti,ab
	24	'anaesthetic drug':ti,ab
	25	'anaesthetics':ti,ab
	26	'anaesthetics, combined':ti,ab
	27	'anaesthetics, dissociative':ti,ab
	28	'anaesthetics, general':ti,ab
	29	'anesthetic':ti,ab
	30	'anesthetic agent':ti,ab
	31	'anesthetic drug':ti,ab
	32	'anesthetics':ti,ab
	33	'anesthetics, combined':ti,ab
	34	'anesthetics, dissociative':ti,ab
	35	'anesthetics, general':ti,ab
	36	'general anaesthetic':ti,ab
	37	'general anaesthetic agent':ti,ab
	38	'general anesthetic':ti,ab
	39	'general anesthetic agent':ti,ab
	40	(#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39)
	41	#15 AND #40
CENTRAL	1	MeSH descriptor: [Anesthesia] explode all trees
	2	MeSH descriptor: [Anesthetics] explode all trees
	3	MeSH descriptor: [Anesthesiology] explode all trees

	4	Anest*:ab,ti,kw
	5	Anaest*:ab,ti,kw
	6	#1 OR #2 OR #3 OR #4 OR #5
	7	MeSH descriptor: [Melanoma] explode all trees
	8	Melanoma*:ab,ti,kw
	9	#7 OR #8
	10	#6 AND #9
Web of science	1	TS=(Anest* OR Anaest*)
	2	TS=(Melanoma*)
	3	#1 AND #2
Virtual Health Library Portal (LILACS and IBECS)	1	mh:("anesthesia")
	2	mh:("anesthesia and analgesia")
	3	mh:("analgesia and anesthesia")
	4	mh:("analgesia")
	5	tw:(anest*)
	6	tw:(analg*)
	7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
	8	mh:(Melanoma)
	9	tw:(Melanoma*)
	10	#8 OR #9
	11	#7 AND #10
International Clinical Trials Registry Platform Portal	In the Advanced Search Title: Anest* OR Anaest* OR Analg* Condition: Melanoma Recruitment status: All	
OpenGrey	1	Anest*
	2	Anaest*
	3	Analg*
	4	#1 OR #2 OR #3
	5	Melanoma*
	6	#4 AND #5

Open Access Theses and Dissertations	1 Anest* 2 Anaest* 3 Analg* 4 #1 OR #2 OR #3 5 Melanoma* 6 #4 AND #5
Google Scholar	anesthesia AND melanoma

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	3-5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☒	☐	125-127
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	61; 128-129
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	7-32
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	293-300
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	127-130
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	115
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	115
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	115
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	81-110
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	115-122
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	132-164
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	165-178
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	179-190
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	191-195
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	196-204
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	196-204
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	228-262
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	147-155
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	205-220
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	214-221
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	214-221; 228-256
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	256-262
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	218-227
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	211-213
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	263-266